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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/986,174	11/07/2001	Nabil Hanna	037003-0280732	4956

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
12/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket_ip@pillsburylaw.com

Office Action Summary	Application No.	Applicant(s)	
	09/986,174	HANNA, NABIL	
	Examiner	Art Unit	
	MISOOK YU	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,23-25 and 27-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,23-25 and 27-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 16, 23-25, and 27-38 are pending and under consideration.

Claim Rejections - 35 USC § 112, Withdrawn

The rejection of claims 16, 23-25, 27-38 under 35 U.S.C. 112, first paragraph, scope of enablement, is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

Claims 16 and 23-31, 33, and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al of record in view of Ozzello et al (IDS filed on 06/14/2004, 1993, Breast Cancer Research and Treatment, vol. 25, pages 263-276).

The claimed invention is drawn to method of treating B cell lymphoma comprising administering to a subject an immunoconjuate comprising an anti-CD20 antibody and interferon-alpha-2a.

Applicant argues that Davis does not suggest or teach making the fusion of anti-CD20 antibody to interferon-alpha-2a, and one of ordinary skill in the art would not have been able to arrive at the claimed invention with a reasonable expectation of success because one of ordinary skill in the art looking at Ozzello on page 267 would likely to conclude that 60,000 times less antibody or 60,000 times more IFN-2-2 alpha would have been required to be effective.

These arguments have been fully considered but found not persuasive because Davis teaches combination therapy of rituximab (anti-CD20 antibody) and IFN-alpha-2a in preclinical studies had been found to be synergistic, therefore, the clinical studies were carried in 38 patients with relapsed or refractory, low-grade or follicular, B-cell

NHL. As applicant correctly calculated at pages 10 and 11 of the Remark's section of the amendment filed on 10/19/2006, the number of molecules of IFN-alpha-2a being administered is 1,600 fold less than the anti-CD20 antibody (i.e. 5 MIU IFN-alpha-2a vs. 375 mg anti-CD antibody) in the clinical studies of Davis. Ozzello et al on page 267 (see below under sub-heading"*Injectables*") teach one of ordinary skill could attach 2 MIU IFN-alpha-2a to 5 mg antibody).

Injectables

The following agents were injected, alone or in combination, in 0.04 ml of PBS containing 0.5% BSA. The doses per injection of each agent are indicated in parentheses:

nIFNα/Mc5: nIFNα (2×10^5 IU) conjugated to Mc5 (5 μg)
nIFNα/IgG$_1$: nIFNα (2×10^5 IU) conjugated to IgG$_1$ (5 μg)
nIFNα: (2×10^5 IU)
nIFNγ: (1×10^5 IU)
Mc5: (50 μg)

Looking at Ozzello et al., one of ordinary skill in the art at the time of the application was filed would be able to attach 5 MIU IFN-alpha-2a to 375 mg anti-CD antibody if necessary. Since Davis teaches that any effective amount is determined first by preclinical trials before proceeding with human subjects, one of ordinary skill in the art would have been able to arrive at the effective dose (note the effective dose range is 10,100 times from 1 microgram to 10 mg) given the teachings of Davis and Ozzello. Ozzello et al., teach that one of ordinary skill in the art would know how to determine a therapeutically effective amount of an immunoconjugate. One of ordinary skill in the art would have been able, using routine in vitro and in vivo methodologies, to establish effective doses of immunoconjugates as taught by, for example, Materials and methods on pages 266-267 in of Ozzello et al., which describe an in vitro screening assay used

to determine therapeutic dosages. One of ordinary skill in the art is well-aware that a precise dose to be employed in the treatment of B cell lymphoma depends on the disease stage, age, sex, medical complications and weight of the individual to be treated, thus determination of an effective dose of the described immunoconjugates for the treatment of B cell lymphoma was routine for a skilled artisan. Therefore it would have been obvious to one of the ordinary skill in the art to make and use an anti-CD20 antibody or a fragment thereof is fused at its carboxy terminus to IFN-alpha-2a in the method for treating the lymphoma with a reasonable expectation of success, since how to make fusion of interferon alfa-2a to anti-CD20 antibody had been well known in the art before the effective filing date of the instant application. One of an ordinary skill would have been motivated to make the fusion to minimize the painful injections by giving one fusion protein instead of two separate injections, and/or purifying one protein instead of two proteins, thus reducing cost and saving time. In addition, Ozzello et al., teach the amount of an interferon required is much less when the interferon is conjugated to a monoclonal antibody binding to an antigen expressed on tumor cells.

In addition, given the instant specification discloses (note page 31, Example 3) that the effective range to be 1 microgram to 10 mg (10,000-fold difference), the difference in dose of Davis (5 MIU IFN-alpha-2a to 375 mg anti-CD20 antibody) to that of Ozzello (2 MIU IFN-alpha-2a to 5 mg) is only about 30-fold, much less than the 10,000-fold difference contemplated in the instant specification on page 31.

Claims 25, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al of record in view of Ozzello et al (IDS filed on 06/14/2004, 1993, Breast Cancer Research and Treatment, vol. 25, pages 263-276) as applied to claim 16 and 29 and further in view of Shan et al., (IDS NNNR filed on 11/10/2004, 1999, J. Immunol. 162, pages 6589-95).

Applicant argues that based on the dosing issues discussed with respect to Ozzello and Davis above, the claimed invention is not obvious. This argument has been fully considered but found unpersuasive because the instant specification does not disclose any unobvious dose of applicant's own other than saying that the doses taught by the two references would not work.

Claims 25, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al of record in view of Ozzello et al (IDS filed on 06/14/2004, 1993, Breast Cancer Research and Treatment, vol. 25, pages 263-276) as applied to claim 16 and 29 and further in view of Haisma et al., IDS IIR filed on 11/10/2004, 1998, Blood 92, 184-90

Applicant argues that based on the dosing issues discussed with respect to Ozzello and Davis above, the claimed invention is not obvious. This argument has been fully considered but found unpersuasive for reasons given above.

Claims 25, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al of record in view of Ozzello et al (IDS filed on 06/14/2004, 1993, Breast Cancer Research and Treatment, vol. 25, pages 263-276) as applied to claim 16 and 29

and further in view of V0se et al., IDS filed on 06/12/2007, J. Clin. Oncol., (Abstract), March 2000.

Applicant argues that based on the dosing issues discussed with respect to Ozzello and Davis above, the claimed invention is not obvious. This argument has been fully considered but found unpersuasive for reasons given above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MISOOK YU
Primary Examiner
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